REMARKS

Claims 25-41 and 44-56 are pending. Reconsideration of the application is requested in view of the remarks which follow.

Claim Rejections

For the sake of brevity, the rejections under 35 USC §103(a) are summarized below and addressed in combination.

Claims 25-26, 29-30, 35-41 and 44-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malvolti et al. (WO 03004005) in view of Nikolaizik et al. (Bronchial constriction after nebulized tobramycin preparations and saline in patients with cystic fibrosis) and Hughes et al. (*The Lancet*, 2003. Use of isotonic nebulised magnesium sulphate as an adjuvant to salbutamol in treatment of severe asthma in adults: randomized placebo-controlled trial).

Claims 25-26, 29-30, 36-41 and 44-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Montgomery (6,083,922) in view of Nikolaizik et al. and Hughes et al.

Claims 27-28 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malvolti et al. in view of Nikolaizik et al. and Hughes et al. as applied to claims 25-26, 29-30, 35-41, 44-56 above, and further in view of Wiedmann et al. (5,747,001).

Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Malvolti et al. in view of Nikolaizik et al. and Hughes et al. as applied to claims 25-26, 29-30, 35-41, 44-56 above, and further in view of Azria et al. (5,759,565).

Each of the rejections is traversed. The cited documents, even in the stated combinations, fail to teach or suggest the features of the present invention in any manner sufficient to sustain any one of the rejections.

Applicant provides the following comments concerning the cited references and the knowledge of one of skill in the art at the time of filing of the instant application regarding the use of nebulized magnesium, tobramycin, or both.

The existence of reports mentioning bronchoconstriction upon tobramycin inhalation, as mentioned by Nikolaizik, is acknowledged. However, it is unclear if the observed bronchoconstriction is related to certain formulation excipients, particularly sodium metabisulphate and phenol. For example, the last portion of the first paragraph in the Nikolaizik Discussion at page 10 states:

> The tobramycin preparation used in our study contained **anti-oxidants and preservatives which also cause bronchial obstruction**. Therefore, it would be of clinical relevance to find out if preservative-free preparations are less irritating. (emphasis added)

Based on the teachings of the reference cited by the Examiner, it is likely that an agent other than tobramycin caused the reaction observed in patients. A reference must be taken as a whole, including portions that teach away from the instantly claimed invention.

The suggestion that the reaction to tobramycin administration is actually a reaction to the preservatives, rather than the tobramycin, is supported by a number of references. For example, Smith et al. (*J Cyst Fibros*. 2002; 1:189-93, abstract enclosed) teaches that:

> Successful drug delivery [of tobramycin] also depends upon a formulation that does not provoke bronchoconstriction, which demands a formulation that is **both preservative free, and osmotically and pH balanced** (emphasis added).

Alothman et al. (Chest. 2002;122:930-4, copy enclosed) performed a study in children with cystic fibrosis in which they compared administration of an inhaled

preservative-free with an inhaled preservative containing (originally for intravenous administration) tobramycin formulation to children at high risk (HR) or low risk (LR) for bronchospasm, essentially the study that Nikolaizik suggested should be performed. Based on this study, Alothman et al. concluded that:

> Both preparations [of tobramycin] caused significant bronchoconstriction in the HR group, and the **preservative-containing IV preparation caused more bronchospasm in LR group than the preservative-free solution**. Heightened airway reactivity in children with CF places them at risk of bronchospasm from inhalation therapy. (abstract, emphasis added)

These studies confirm the suggestion of Nikolaizik that the bronchoconstriction was most likely a result of the preservatives rather than the tobramycin.

Alothman, being one of skill in the art, discusses the results from their study in view of previous studies. Particularly, on page 932, second column, Alothman notes:

> The bronchospasm seen in the LR group when exposed to the preparation containing preservatives but with less tobramycin would be in **keeping with the earlier suggestions of Beasley et al,[14] that the preservatives rather than the drug were likely to be responsible for the observed bronchoconstriction**.... **Contrary to suggestions by Nikolaizik et al**,[7] **the concentration of tobramycin alone seems not to have been a factor**, since the tobramycin dose in the preservative-free formulation was threefold higher (60 mg/mL vs 20 mg/mL) than that in the IV preparation, and yet did not induce bronchospasm in the LR group. Given the identical inhalation protocol, the high concentration would be expected to give rise to a much higher lung deposition of tobramycin, suggesting that differences in airway surface tobramycin concentration between the two preparations would not explain the differences. (emphasis added)

Further, in the second column on page 933 it is noted:

> Finally, data from the HR group lend further credence to earlier speculations on **the role of the inherent airway hyperreactivity in patients with CF as a predictive risk factor for bronchoconstriction from inhaled solutions**.[10,18] In this group, the prevalence of bronchoconstriction was independent of the preparation administered. A relatively high prevalence of bronchospasm has been demonstrated in patients with CF with advanced lung disease following the inhalation of normal saline solution.[7] **Combined with the data of the present study,**

this suggests that the deposition of droplets in the airway may give rise to bronchospasm in CF independent of the content of the droplet. (emphasis added)

Therefore, having performed the experiment suggested by Nikolaizik et al, Alothman et al. concluded that it is the **preservatives, not the tobramycin, that results in the airway reactivity**. Further, there are certain individuals who will react to administration of any agent by nebulization to the lungs, **independent of the content of the droplet**. Therefore, based on the knowledge of those of skill in the art, one would not be motivated to add magnesium to a tobramycin formulation to provide reduced irritation. Instead, one would administer a preservative free solution of tobramycin, and administer an agent known to reduce bronchospasm, e.g., albuterol, as in Alothman et al. when needed.

In inhalation therapy, one hesitates to include excipients that might not be necessary; therefore, the skilled person would not add magnesium to prevent an effect caused by an additive that could readily be excluded from the formulation, especially where it is not known if the desired effect would be obtained. In trying to reduce an undesirable response, one would be motivated to remove components, particularly non-therapeutically active components known to cause irritation, rather than add new components. An obviousness rejection must consider what one of skill in the art would be **motivated** to do, not simply what one could possibly do. The existence of all of the components of the invention in the cited art cannot alone provide motivation to combine the elements.

Applicant acknowledges that magnesium has been evaluated as a bronchodilating agent. However, literature clearly demonstrates that the effect of **inhaled magnesium** (in contrast to intravenously administered magnesium) is not clear. Also, much of the relevant literature refers to the use of magnesium in **asthma**, but not to the use of magnesium to prevent **formulation-induced bronchoconstriction**. The etiology of formulation-induced bronchoconstriction and asthma (and tuberculosis) are distinct. Compounds or methods for the prevention or

treatment of one would not necessarily be expected to be useful for the treatment of the other.

Further, the concentration and dosage of magnesium that should be delivered by inhalation are not clear from the cited art. According to Hughes, a concentration of 250 mmol/L, resulting in an isotonic solution with osmolality of 289 mOsmol was used. However, as Mg sulphate is expected to dissociate in two ions when dissolved in water, the calculated osmolality should be approximately 500 mOsmol/L. It is not clear from publication why osmolality mentioned by Hughes is much lower. The fact that 151 mg / 2.5 ml was used indicates that Mg sulphate heptahydrate had been used (MW of Mg sulphate heptahydrate is 246.46 g/mol, in that case 151 mg / 2.5 ml corresponds to a theoretical concentration of 245 mmol/L). Other magnesium sulphate concentrations mentioned in the Mohammed review (from studies dated before priority date of current application, irrespective if they were successful or not) are 64 mg/ml (Bessmertny), 75 mg/ml (Nannini), 32 mg/ml (Mangat) and 280 mmol/ml (Meral).

If it is assumed that Hughes made a correct statement regarding osmolality, it can be calculated from the tobramycin concentrations given if this concentration of Mg sulphate can still be added without exceeding the maximum preferred osmolality claimed. The claimed tobramycin concentrations of 80 and 120 mg/ml have an osmolality between 171 and 257 mOsmol/L (no dissociation and MW of tobramycin is 467.5 g/mol). This leaves between 129 and 43 mOsmol/L for additional excipients (to arrive at an osmolality of 300 mOsmol as mentioned in claim 34 and known to be best tolerable as isotonic to body fluids). According to the data given by Hughes (250 mmol/L corresponds to 289 mOsmol), the corresponding magnesium sulphate concentration would range between 112 and 37 mmol/L or between 27 and 9 mg/ml. This is clearly lower than what is described and evaluated in the prior art (see also Mohammed review).

Not relying on the data from Hughes, but on the theoretical dissociation in two ions, the following range can be calculated: 129 and 43 mOsmol/L correspond with 64.5

and 21.5 mmol/L or 16 and 5 mg/ml magnesium sulphate. In this case, the difference with the concentrations tested in inhalation studies is even larger. This is assuming that there are no other components in the formulation that would effect osmolality.

Taking into consideration that the reported results of inhaled magnesium are already uncertain, a skilled person will not have a reasonable expectation of success by reducing the magnesium concentration to the above calculated concentrations, far below what is indicated in the prior art.

According to calculations starting from the instantly claimed tobramycin concentration, it becomes clear that the magnesium concentrations that can be applied in the claimed tobramycin formulations can never be as high as in the studies where inhaled magnesium has been studied.

Around the date of the filing of the instant application, the effects of inhaled magnesium sulphate were still not known as demonstrated by Aggarwal et al. (*Emerg. Med. J.* 2006. 23:258-362, copy enclosed). The authors set forth the following objective for the study:

> **To test the hypothesis** that combined administration of multiple doses of nebulized salbutamol and magnesium sulphate provides additional benefit compared with salbutamol alone in adult patients with acute asthma (abstract, emphasis added).

Having set forth that objective, the effects of inhaled magnesium was clearly not known by one of skill in the art at the time of the study. After completing the study, Aggarwal et al. concluded:

> This study suggests that **there is no therapeutic benefit of adding magnesium sulphate to salbutamol nebulization** in the treatment of patients with acute severe or life threatening asthma (abstract, emphasis added).

The background section of Aggarwal et al. discusses the uncertainty in the field regarding the effects of nebulized magnesium alone or in combination with salbutamol, the shortcomings of the studies, the conflicting results from the studies, and the need for

further analysis provided by the study. Therefore, at the time of the filing of the instant application, the effects of nebulized magnesium, alone or in combination with other nebulized agents, was not known to one of ordinary skill in the art. Obviousness rejections must consider the knowledge of those of skill in the art which would include Aggarwal and Smith, in addition to the references cited in the Office Action.

In the Office Action, Malvolti et al. is relied upon to teach optimized formulations of tobramycin for aerosolization in the form of additive-free, isotonic solution whose pH has been optimized to ensure adequate shelf-life at room temperature. The Office Action notes that in the optimization, Malvolti decreased the sodium concentration, and therefore the osmolality, to **¼ normal saline** to provide an improved effect. The Office Action notes that Malvolti does not suggest the use of magnesium or calcium in the formulation, and relies upon Nikolaizik et al. and Hughes et al. to overcome this deficiency. **However, there can be no motivation to increase the osmolality of the formulations of Malvolti, having optimized administration of tobramycin by reducing the osmolality**, particularly to isotonic magnesium as suggested by Hughes.

Further, there can be no motivation to limit the sodium concentration to less than 2 mg/ml as instantly claimed. The Office Action asserts that based on the teachings of Montgomery of the advantages of the use of 1/4 normal saline because it allows for higher amounts of tobramycin being delivered, it would have been clear to one of ordinary skill in the art that lower concentrations of sodium chloride in the solution formulation would be beneficial. Applicant submits that there can be no motivation to **both** further decrease the sodium concentration based on the teachings of Malvolti to the claimed amounts, to further improve administration, and to add magnesium or calcium, which would be expected to decrease the efficacy of delivery. The rejection cannot reasonably assert that it would both be obvious to decrease the salt concentration/ osmolality and increase the salt concentration/ osmolality.

Further, as discussed above, Nikolaizik et al. suggests that the irritation experienced upon administration of tobramycin is a result of preservatives, and not

tobramycin itself. This suggestion is confirmed by each of Smith and Alothman. Further, the concentrations of magnesium used in the prior art, would result in a formulation with an osmolality substantially higher than the claimed maximal osmolality, especially when further including saline as required by Malvolti. The ability of salbutamol to prevent tobramycin formulation–induced constriction provides no motivation to include magnesium in a formulation with tobramycin, particularly when one of skill in the art would not expect that the tobramycin is causing airway constriction.

The effect of Hughes observed with administration of salbutamol with severe asthma cannot provide motivation to add magnesium to tobramycin for nebulized administration. Salbutamol is a rapid-acting, short-acting β2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease. Tobramycin sulfate is an aminoglycoside antibiotic used to treat various types of bacterial infections, particularly Gram-negative infections. There is essentially no commonality in the mechanism of actions of the drugs, the subjects to be treated using the drugs, or the events to prompt treatment with the drugs. Hughes observed an increase in FEV_1 in response to treatment of asthma with a combination of salbutamol and magnesium as compared to salbutamol alone. Tobramycin, being an antibiotic, would not be expected to have any rapid action to alter FEV_1. Therefore, there can be no expectation that magnesium would have any effect on a relatively slow acting agent such as an antibiotic.

Montgomery is relied upon to teach a method of treating chronic tuberculosis using a preservative-free concentrated tobramycin aerosol formulation allegedly containing 40 to 800 mg of tobramycin in 5 ml of quarter normal saline (8-160 mg/ml). The tobramycin formulations comprising 60 mg/ml of 1/4 NS have an osmolarity in the range of 165-190 mOsm/l and a pH between 5.5 and 7.0. As with Malvolti, Montgomery is said to teach the use of ¼ saline for improved administration of tobramycin as compared to administration in normal saline, and is said to not teach administration of calcium or magnesium.

The combination of Montgomery with Hughes fails for the same reason as in the combination of Malvolti and Hughes. Montgomery teaches the advantages of reducing the osmolality of the formulation by reducing the amount of saline in the formulation to ¼ normal saline. Applicant submits that there can be no motivation to **both** further decrease the sodium concentration based on the teachings of Montgomery to the claimed amounts, to further improve administration, and to add magnesium or calcium, per Hughes which would be expected to decrease the efficacy of delivery. The rejection cannot reasonably assert that it would both be obvious to decrease the salt concentration/ osmolality and increase the salt concentration/ osmolality.

Further, tuberculosis, asthma, and irritant induced bronchoconstriction are substantially different conditions. The effect of an agent in one of the conditions cannot predict a similar outcome with other conditions using the same agent.

Wiedmann et al. is relied upon in a rejection of dependent claims to allegedly teach an aerosol comprising droplets of an aqueous dispersion of nanoparticles, comprising an active agent having a surface modifier on the surface thereof (see abstract). The said modifiers include calcium stearate, magnesium aluminum silicate, lecithin (phosphatides), n-dodecyl R-D-maltoside and tyloxapol (see cols. 3-4). Wiedmann cannot make up for the deficiencies in the combination of Malvolti et al., Nikolaizik et al., and Hughes et al. for at least the reasons set forth above. Therefore the rejection cannot stand.

Azria et al. is relied upon in a rejection of dependent claims to teach pharmaceutical compositions for nasal administration, comprising an active and a surfactant in a liquid carrier. Azria cannot make up for the deficiencies in the combination of Malvolti et al., Nikolaizik et al., and Hughes et al. for at least the reasons set forth above. Therefore the rejection cannot stand.

Finally, the Office Action states that absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention.

Applicant respectfully disagrees. References provided by Applicant and discussed above clearly demonstrate that one of skill in the art would not have known or been reasonably able to expect any particular effect of nebulized magnesium that would be observed upon co-administration with tobramycin based on the uncertainty in the art for example as shown by Aggarwal. Further, a rejection cannot reasonably assert that it would have been obvious to both decrease the osmolality and increase the osmolality of a solution for delivery by nebulization.

As the references cannot be properly combined they cannot render obvious the instantly claimed invention. Withdrawal of the rejections is respectfully requested.

In view of the above amendments and remarks, Applicant believes the pending application is in condition for immediate allowance.

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Respectfully submitted,

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